AMENDMENTS TO THE SPECIFICATION:

Please replace Table 3 with the following Table.

Residues that Determine Specificity															Substrate Specificity					
	S4					S3		S2			S1									Seq ID No.
	171	174	180	215	Cys 168 Cys 182	192	218	99	57	60s loop	189	190	226	Cys 191 Cys 220		P4	P3	P2	P1	
Granzyme B	Leu	Tyr	Glu	Tyr	14	Arg	Asn	Ile	His	6	Gly	Ser	Arg	No	Granzyme B	Ile Leu	Glu	X	Asp	23
Granzyme A	Asn	Val	Met	Phe	17	Asn	Leu	Arg	His	7	Asp	Ser	Gly	yes	Granzyme A	Ile Val	Ala Gly	Asn Asp Glu	Arg	24
Granzyme M	Arg	Ser	Met	Phe	15	Lys	Arg	Leu	His	8	Ala	Pro	Pro	Yes	Granzyme M				Leu Met	
Cathepsin G	Phe	Ser	Gln	Tyr	13	Lys	Ser	Ile	His	6	Ala	Ala	Glu	no	Cathepsin G	X	X	Val Leu	Phe Lys	25
MTSP-1	Leu	Gln	Met	Trp	13	Gln	Asp	Phe	His	16	Asp	Ser	Gly	Yes	MTSP-1	Arg HΦ	HΦ Arg	Ser Thr	Arg Lys	26
Neutrophil Elastase	-	-	-	Tyr	5	Phe	Gly	Leu	His	10	Gly	Val	Asp	Yes	Neutrophil Elastase	Arg Met Tyr	Gln Glu	Pro Ala	Val Ala Ile	27
Chymase	Phe	Arg	Gln	Tyr	12	Lys	Ser	Phe	His	6	Ser	Ala	Ala	Yes	Chymase	X	Glu Ala	X	Phe Tyr	28
alpha-Tryptase	Tyr	Ile	Met	Trp	22	Lys	Glu	Ile	His	9	Asp	Ser	Gly	Yes						
beta-Tryptase (I)	Tyr	Ile	Met	Trp	22	Gln	Glu	Val	His	9	Asp	Ser	Gly	Yes						
beta-Tryptase (II)	Tyr	Ile	Met	Trp	22	Lys	Glu	Thr	His	9	Asp	Ser	Gly	Yes						
Chymotrypsin	Trp	Arg	Met	Trp	13	Met	Ser	Val	His	7	Ser	Ser	Gly	Yes	Chymotrypsin	X	X	Val Pro	Phe Tyr	29
Easter	Tyr	Ser	Gln	Phe	16	Arg	Thr	Gln	His	14	Asp	Ser	Gly	Yes	Easter	Ile Val	Glu Ala	Val Leu	Arg	30
Collagenase	Tyr	Ile	-	Phe	12	Asn	Ala	Ile	His	8	Gly	Thr	Asp	Yes	Collagenase				Arg	
Factor Xa	Ser	Phe	Met	Trp	13	Gln	Glu	Tyr	His	8	Asp	Ala	Gly	Yes	Factor Xa	X	X	Gly	Arg	31
Protein C	Met	Asn	Met	Trp	13	Glu	Glu	Thr	His	8	Asp	Ala	Gly	Yes						
Plasma Kallikrein	Tyr	Gln	Met	Tyr	13	Arg	Pro	Phe	His	11	Asp	Ala	Ala	Yes	Plasma Kallikrein	HΦ	X	Phe Tyr	Arg	32
Plasmin	Glu	Arg	Glu	Trp	15	Gln		Thr	His	11	Asp	Ser	Gly	Yes	Plasmin	Lys	X	Trp Phe	Lys	33
Trypsin	Try	Lys	Met	Trp	13	Gln	Tyr	Lue	His	6	Asp	Ser	Gly	Yes						
Thrombin	Thr	Ile	Met	Trp	13	Glu	Glu	Lue	His	16	Asp	Ala	Gly	Yes	Thrombin	Phe Leu	X	Pro	Arg	34
tPA		Thr	Met	Trp	15	Gln		Tyr	His	11	Asp	Ala	Gly	Yes	tPA	X	Thr Ser	Gly Ser	Arg	35
uPA	His	Ser	Met	Trp	15	Gln	Arg	His	His	11	Asp	Ser	Gly	Yes	uPA	X	Thr Ser	Ser Ala	Arg	36

Please replace the paragraph at page 21, lines 3-17 with the following amended paragraph.

Granzyme B is a member of the family of chymotrypsin fold serine proteases, and has greater than 50% identity to other members of the granzyme family including granzymes C-G, cathepsin G, and rat mast cell protease II. The protein is a sandwich of two six stranded, anti-parallel β-barrel domains connected by a short α-helix. The catalytic triad is composed of Asp102, His 57 and Ser 195. The surface loops are numbered according to the additions and deletions compared to α-chymotrypsin and represent the most variable regions of this structural family. The determinants of specificity are defined by the three-dimensional structure of rat granzyme B in complex with ecotin ~~[IEPD]~~ (IEPD; SEQ ID NO:21), a macromolecular inhibitor with a substrate-like binding loop (Waugh *et al.*, Nature Struct.

Biol). These structural determinants of specificity include Ile99, Arg192, Asn218, Tyr215, Tyr174, Leu172, Arg226, and Tyr 151, by chymotrypsin numbering. Interestingly, the other members of the granzyme family of serine proteases share only two of these amino acids with granzyme B. They are Tyr 215 and Leu 172, two residues that vary very little across the entire structural family. This suggests that while the sequence identity of the granzymes is high, their substrate specificities are very different

Please replace Table 5 with the following Table .

Specificity Profile					
Mutant	**P4**	**P3**	**P2**	**P1**	**SEQ ID NO.**
Wildtype	Ile/Val	Glu	X	Asp	23
I99F	Ile/Val	Glu	X	Asp	37
I99A	Ile/Val	Glu	**Phe**	Asp	38
I99K	Ile/Val	Glu	X	Asp	39
N218A	Ile/Val	X	X	Asp	40
N218T	Ile/Val	**Ala/ Ser**	X	Asp	41
N218V	Ile/Val	**X**	X	Asp	42
R192A	Ile/Val	Glu	X	Asp	43
R192E	Ile/Val	**Lys/ Gln/ Ser**	X	Asp	44
Y174A	**Ile/Val /Leu**	Glu	X	Asp	45
Y174V	Ile/Val	Glu	X	Asp	46
I99A/N218A	**Phe/ Leu /Ile/Val**	**Ala/ Ser**	**Phe**	Asp	47
R192A/N218A	Ile/Val	**Ala/ Gln/ Ser**	X	Asp	48
R192E/N218A	Ile/Val	**Arg Lys Ala**	X	Asp	49

Please replace Table 6 with the following Table.

Residues that Determine Specificity														Substrate Specificty					
	Active Site residues			S3		S2					S1								Seq ID No.
	25	159	175	61	66	66	133	157	160	205	19	20	158		P4	P3	P2	P1	
Cathepsin G	Cys	His	Asn	Glu	Gly	Gly	Ala	Met	Gly	Ala	Gln	Gly	Asp	Cathepsin G	X	X	Phe Trp	Arg Lys	50
Cathepsin V	Cys	His	Asn	Gln	Gly	Gly	Ala	Leu	Gly	Ala	Gln	Lys	Asp	Cathepsin V	X	Pro X	Trp Tyr	X	51

																		Phe		
Cathepsin K	Cys	His	Asn	Asp	Gly	Gly	Ala	Leu	Ala	Leu	Gln	Gly	Asn		Cathepsin K	X	X	Leu Pro	Arg Lys	52
Cathepsin S	Cys	His	Asn	Lys	Gly	Gly	Gly	Val	Gly	Phe	Gln	Gly	Asn		Cathepsin S	X	Arg X	Val Leu Met	Lys Arg	53
Cathepsin F	Cys	His	Asn	Lys	Gly	Gly	Ala	Ile	Ala	Met	Gln	Gly	Asp		Cathepsin F	X	X	Leu	Lys Arg	54
Cathepsin B	Cys	His	Asn	Asp	Gly	Gly	Ala	Gly	Ala	Glu	Gln	Gly	Gly		Cathepsin B	X	Pro X	Val Phe Tyr	Arg Lys	55
Papain	Cys	His	Asn	Tyr	Gly	Gly	Val	Val	Ala	Ser	Gln	Gly	Asp		Papain	X	Pro X	Val Phe Tyr	Arg Lys	56
Cruzain	Cys	His	Asn	Ser	Gly	Gly	Ala	Leu	Gly	Glu	Gln	Gly	Asp		Cruzain	X	Arg X	Leu Phe Tyr	Arg Lys	57

Please replace the paragraphs at page 53, line 2 through page 54, line 3 with the following amended paragraphs.

I99A/N218A granzyme B cleaved and inactivated full length caspase-3. Purified caspase-3 (2 μM) was incubated with no protease, 100 nM of wildtype granzyme B, or 1 μM I99A/N218A granzyme B for 18 hours in granzyme B activity buffer. 10 μL of each reaction was diluted in 90 μL of caspase-3 activity buffer and caspase-3 activity was assayed by cleavage of Ac-DEVD-AMC (SEQ ID NO:22). Figure 6A shows a graph of caspase-3 activity plotted against time. I99A/N218A granzyme B inactivated caspase-3 to a very low level of activity. Wild-type granzyme B inactivated caspase-3 more than control, but did not have the effect that the mutant has on caspase-3 activity. This is also shown in Figure 6B, where Vmax of caspase-3 activity is shown derived from the data represented in Figure 6A. Vmax in the presence of the mutant granzyme B is approximately zero, wherein the wild-type only halves the Vmax relative to control.

The mutant granzyme B was also effective in inhibiting caspase-3 activity and apoptosis in cell lysates containing caspase-3. In Figure 7A, indicated amounts of I99A/N218A granzyme B was added to cell lysates and incubated for 18 hours. Caspase-3 activity was then assayed by adding a fluorogenic substrate (Ac-DEVD-AMC) (SEQ ID NO:22) to a final concentration of 200 μM. At low concentrations the mutant activates caspase-3 by cleaving at the activation sequence (SEQ ID NO:4), but at high concentrations it inhibits caspase-3 by cleaving at the inactivation sequence. Thus, I99A/N218A granzyme B induces apoptosis at low concentrations but inhibits apoptosis at high concentrations. Figure 7A plots caspase-3 activity against increasing concentrations of I99A/N218A mutant granzyme B. As the concentration of the mutant granzyme B was increased in cell lysates, the caspase-3 activity decreased.

Apoptosis was induced in cell lysates by adding 100 nM of wildtype granzyme B, which activates caspase-3 by cleaving at the activation sequence, with or without the

indicated amount of I99A/N218A granzyme B, and incubated for 18 hours. Caspase-3 activity was assayed by cleavage of Ac-DEVD-AMC (SEQ ID NO:22). Data was normalized for the background caspase-3 activity induced by the I99A/N218A granzyme B. 100 nM of wild-type granzyme B was added to cell extracts in all samples, with or without increasing concentrations of I99A/N218A granzyme B as indicated in Figure 7B. As shown in Figure 7B, the mutant granzyme B antagonized the effect of wildtype granzyme B to induce apoptosis by inactivating caspase-3. Figure 7B shows a graph with the fraction of caspase-3 activity with varying concentrations of mutant granzyme B in the presence of 100 nM wild-type granzyme B. With increasing concentrations of mutant granzyme B, the caspase-3 activity decreased below the level it was in the presence of wild-type granzyme B alone.